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【 EDITORIAL 】

Galectin-3 as an Arrhythmogenic Predictive Marker for Heart Failure

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In this issue of *Internal Medicine*, Makimoto et al. (1) assessed the utility of circulating galectin-3 (Gal-3) as an independent indicator of the prognosis of heart failure (HF) patients with implantable cardioverter-defibrillators (ICDs). To assess the prognosis of HF, they defined the implementation of appropriate ICD therapy (on the occurrence of lethal ventricular arrhythmic events) as the primary endpoint and unplanned HF hospitalization as the secondary endpoint. A receiver operating characteristic analysis demonstrated 83% sensitivity and 68% specificity for the occurrence of lethal ventricular arrhythmic events with a Gal-3 cut-off value of 13.1 ng/mL (AUC=0.82). A Kaplan-Meier analysis showed that patients with Gal-3>13.1 ng/mL had significantly higher incidences of both ventricular arrhythmic events and HF hospitalization than patients with lower Gal-3 levels. A Cox regression analysis demonstrated that Gal-3>13.1 ng/mL was an independent predictor of both ventricular arrhythmic events, even after adjusting for previous arrhythmic events. These data indicated the possible utility of circulating Gal-3 levels as an arrhythmogenic predictive marker for HF patients. However, the study has several limitations, including its single-center setting and the small number of patients enrolled. The utility of Gal-3 for risk stratification needs to be further evaluated in large-scale multicenter studies.

Gal-3 is a β-galactoside-binding lectin that plays an important role in regulating inflammation and fibrosis (2). Gal-3 has been known to be involved in a pathological fibrotic mechanism and collagen synthesis by fibroblasts (3) and is reported to be upregulated in various fibrotic diseases, including cardiac fibrosis (4, 5). Elevated levels of circulating Gal-3 were reportedly associated with the incidence of HF events and mortality (6-9). The expression of Gal-3 is increased in activated macrophages and stimulates pathological cardiac remodeling, particularly by inducing cardiac fibroblast proliferation and collagen deposition (8). Thus, Gal-3 seems to contribute to cardiovascular physiological processes, including myofibroblast proliferation, tissue repair, and cardiac remodeling in the setting of HF (5).

In this context, Lau et al. (2) recently explored the question of whether or not Gal-3 inhibition could reduce cardiac fibrosis. They conducted a proof-of-concept randomized placebo-controlled trial of modified citrus pectin (MCP), a direct Gal-3 inhibitor, in hypertensive subjects with elevated Gal-3 levels (≥13.1 ng/mL in men, ≥14.3 ng/mL in women) and assessed biomarkers of collagen metabolism, echocardiographic measures of the cardiac diastolic function, and vascular stiffness. However, contrary to expectations, Gal-3 inhibition did not influence these surrogate measures of cardiac fibrosis. This neutral result may be related to the small sample size, relatively healthy study population, MCP dosage, poor tolerability of the MCP, or study duration (10).

HF is an important public health concern, and the effectiveness of conventional heart failure therapy is limited. Therefore, there is a demand for a new approach to treating HF. Gal-3-targeted HF treatment will likely attract more and more attention in the future.

The authors state that they have no Conflict of Interest (COI).

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